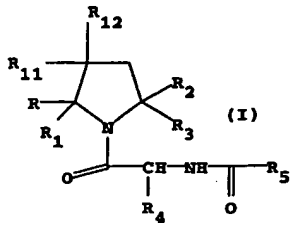
94-242600/30 B03 RHON 93.01.07
RHONE POULENC RORER SA C*FR 2700166-A1
93.01.07 93FR-000078 *(94.07.08)* C07D 207/08, A61K 31/40

New pyrrolidine derivs. with affinity for cholecystokinin and gastrin receptors - are used to treat e.g. psychosis, anxiety, irritable colon syndrome, tumours and pancreatitis.

C94-110768

Addnl. Data: CAPET M, DUBROEUCQ M

Pyrrolidine derivs. of formula (I) and their salts and isomers are new:



(I)

B(5-B1A, 6-D1, 6-D2, 7-D3, 14-C1, 14-D2B, 14-E8, 14-E10C, 14-E11, 14-E12, 14-H1B, 14-J1A1, 14-J1A3, 14-J1A4, 14-J1B3, 14-J1B4, 14-M1A, 14-M1C) .10

R = 1-12C alkyl, 3-12C cycloalkyl or 6-12C polycycloalkyl (all opt. mono or polyunsatd); phenylalkyl (opt. ring-substd. by alkyl, alkoxy and/or halo); diphenylalkyl; cinnamyl; pyridyl, furyl, thienyl, quinolyl, naphthyl or indolyl (all opt. substd. by one or more alkyl); or phenyl (opt. substd. by halo, alkyl, alkoxy, OH, NO_2, amino, mono- or di alkylamino, alkoxycarbonyl, $CONR_7R_8$, NHCOMe, CF_3, Ph and/or OCF_3);

R_1, R_3, R_4 = H or alkyl;

R_2 = $(CH_2)_n$- COR_6, $(CH_2)_mOCOR''_6$, $-(CH_2)_mNR_9R_{10}$ or oxazolinyl (opt. substd. by alkyl, and/or alkyl-3-oxadiazolyl);

R_5 = phenyl (opt. substd. by halo, alkyl, alkoxy, and/or alkylthio),or naphthyl, indolyl, quinolyl, or phenylamino (all opt. phenyl-substd. by halo, alkyl, alkoxy, alkylthio, CF_3, COOH, alkoxycarbonyl, OH, NO_2, amino, acyl, CN, sulphamoyl, carbamoyl, hydroxyimino alkyl, alkoxyiminoalkyl, hydroxyamino carbonyl, alkoxyaminocarbonyl, tetrazol-5-yl, tetrazol-5-ylalkyl, trifluoromethylsulphonamido, alkylsulphinyl, mono- or polyhydroxyalkyl, sulpho, alk-O-CO-alk, alk-COOX,

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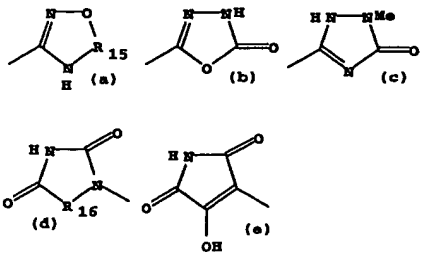
alk-O-alk, alk^1-COOX, O-alk-COOX, CH=CHCOOX, $COCO_2X$, $alkSO_3H$ (or its salt), CH=CH-alk^1, C(=NOH)CO_2X, S-alk-CO_2X, SO-alk-CO_2X, SO_2-alk-CO_2X, OCH_2alk^1-COOX, CX=NO-alk-CO_2X, alk-N(OH)-CO-alk, $alkSO_2H$, SO_2NHCOR_{13}, $SO_2NHSO_2R_{13}$, $CONHCOR_{13}$, $CONHSO_2R_{13}$, $B(OH)_2$, $C(NH_2)$=NOH, SO_2NHR_{14}, $CONHR_{14}$, 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl or a gp. of formula (a)-(e)):



R_6 = OH, alkoxy, cycloalkoxy, cycloalkyl-alkoxy, phenyl or NR_9R_{10};

R''_6 = alkoxy, cycloalkoxy, cycloalkylalkoxy, phenyl or NR_9R_{10};

R_7 = H, alkyl, phenylalkyl or phenyl (opt. substd. by halo, alkyl, alkoxy and/or alkylthio);

R_8 = alkyl, phenylalkyl or phenyl (opt. substd. by halo, alkyl, alkoxy and/or alkylthio); or

NR_7R_8 = mono- or polycyclic opt. unsatd. heterocyclyl contg. 4-9C atoms and one or more O or N atoms and opt substd. by one or more alkyl;

R_9 = H, alkyl, cycloalkylalkyl, cycloalkyl, phenylalkyl or phenyl (opt. substd. by halo, alkyl, alkoxy, and/or alkylthio),

R_{10} = alkyl, cycloalkyl, cycloalkylalkyl; phenylalkyl, or phenyl (opt. substd. by halo, alkyl, alkoxy and/or alkylthio); or

NR_9R_{10} =mono- or polycyclic opt. unsatd. heterocyclyl contg. 4-9C and one or more O,N and S, and opt. substd. by one or more alkyl;

R_{11} = H, alkyl or phenylalkyl;

R_{12} = alkyl, phenylalkyl, phenylsulphonyl, $(CH_2)_pCOR_{17}$, CN, CXO, CX=NOH, CX = NOalkCOOX, CHXOH, CHXOCOalk, NH_2 or NHCOalk;

R_{13} =alkyl, cycloalkyl, CF_3, or phenyl (opt. substd. by CN, NO_2, amino, halo and/or alkoxy);

R_{14} = tetrazol-5-yl;

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R_{15} = CO or SO;

R_{16} = O or CO;

R_{17} =OH, alkoxy, cycloalkoxy, cycloalkylalkoxy, phenyl, phenylalkoxy, alkyl or NR_9R_{10};

n = 0-2;

m = 1 or 2;

p = 0 or 1;

X = H, alkyl, or phenyl alkyl;

alk = alkyl or alkylene; and

alk^1 = hydroxyalkyl, hydroxyalkylene, alkoxyalkyl or alkoxyalkylene; unless otherwise stated all alkyl moieties contain 1-4C; acyl contain 2-4C; and cycloalkyl contains 3-6C.

USE

(I) have strong affinity for cholecystokinin (CCK) and gastrin receptors. They are particularly useful in the treatment and prevention of disorders due to CCK and gastrin in the nervous system and GI tract. They are used to treat and prevent psychoses, anxiety, depression, neurodegeneration, panic attacks, Parkinson's disease, tardive dyskinesia, irritable bowel syndrome, pancreatitis, ulcers, intestinal motility disorders, certain tumours sensitive to CCK, memory dysfunction, chronic withdrawal and abuse of alcohol or drugs, as pupil constrictors, analgesics or as potentiators for analgesics (both narcotic and non narcotic), and as appetite regulators.

DOSAGE

Dosage is pref. oral at 0.05-1g/day in unit doses of 10-500 mg.

ADVANTAGE

(I) have low toxicity e.g. LD_{50} of more than 40 mg/kg in mice.

PREPARATION

4 methods are claimed e.g. as follows: (a) (I; R_5=$R_5{}^1$) is prepd. by reacting a carbamic acid deriv. obtd. opt. in situ by reaction of a carbonic acid deriv. chosen from N,N^1-diimidazolecarbonyl, phosgene, triphosgene and p nitrophenylchloroformate with a pyrrolidine cpd. of formula (II), with an aniline deriv. where the phenyl ring is opt. substd. by Q, and opt. salifying.

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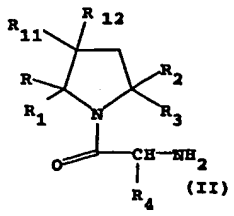
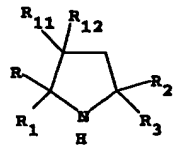


(II)

R_5^1 = phenylamino (opt. ring substd.)
Q = halo, alkyl, alkoxy, alkylthio, CF_3, COOH, alkoxycarbonyl, OH, NO_2, amino, acyl, CN, sulphamoyl, carbamoyl, hydroxyiminoalkyl, alkoxyiminoalkyl, hydroxyaminocarbonyl, alkoxyaminocarbonyl, tetrazol-5-yl, tetrazol-5-ylalkyl, trifluoromethylsulphonamido,alkylsulphinyl, mono- or polyhydroxyalkyl, S, alk OCOalk, alkCOOX, alk-O-alk, alk^1-COOX, O-alkCOOX, CH=CHCOOX, $COCO_2X$, $alkSO_3H$ (as its salt), CH=CH-alk^1, C(=NOH)-COOX, S-$alkCO_2X$, SO-alk-COOX, SO_2-alk-COOX, OCH_2-alk^1-COOX,

CX=NO-alk-CO_2X, alk-N(OH)-CO-alk, 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl, $alkSO_2H$, SO_2NHCOR_{13}, $SO_2NHSO_2R_{13}$, $CONHCOR_{13}$, $CONHSO_2R_{13}$, $B(OH)_2$, $C(NH_2)$=NOH, SO_2NHR_{14}, $CONHR_{14}$ or a gp. (a)-(e).

(b)



HOOC -CHR_4 - $NHCOR_5$ (I;n=0; R_2= R_2'; R_6= R_6'; R_5= R_5''; X is not H)

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R_2^1 = $(CH_2)_nCOR_6$;
R_6^1 = alkoxy, cycloalkoxy or cycloalkylalkoxy;
R_5^{11} = phenyl (opt. substd.) naphthyl, indolyl, quinolyl or phenylamino (opt. ring substd. by halo, alkyl, alkoxy, alkylthio, CF_3, NO_2, acyl, CN, sulphamoyl, alkoxycarbonyl, carbamoyl, alkoxyiminoalkyl, alkoxyaminocarbonyl, alk-O-CO-alk, CH=CH-alk^1, alk-O-alk, trifluoromethylsulphonamido, $alkSO_3H$ (or its salt), O-alkCOOX, CH=CHCO_2X, $COCO_2X$, S-$alkCO_2X$, SO-alk CO_2X, SO_2alkCO_2X, OCH_2-alk^1-CO_2X, CX=NOalk-CO_2X, $alkCO_2X$ or alk^1CO_2X); and
cpds. (I) may be interconverted.

EXAMPLE

A soln. of 0.32g tertbutyl 4-benzyl 5-phenyl 2-pyrrolidine carboxylate and 0.31g 2-(3-(3-benzyloxycarbonyl-phenyl)ureido) acetic acid in 25ml acetonitrile was treated with 0.2g N,N'-dicyclohexylcarbodiimide at 20 ° C. The mixt. was stirred for 72 hrs. at 20 ° C. and worked up to give 0.54g (2S,4S,5R)tert-butyl-1-(2-(3-(3-benzyloxycarbonylphenyl)ureido) acetyl)-4-benzyl-5-phenyl pyrrolidinecarboxylate.

A soln. of 0.54g. of this prod. in 25ml EtOAc was treated with 0.1g 10% Pd/C. The suspension was stirred for 18 hrs. at 20 ° C. under H_2 (130KPa). The catalyst was filtered off and the mixt. was worked up and chromatographed to give 0.36g free acid.

In tests (I) have IC_{50} value of < 1000nM for inhibition of binding to CCK receptors. (48pp1858DwgNo.0/0)

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